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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,164	12/20/2001	Benjamin J. Metcalf	33,484-00	3977

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FLS

Office Action Summary	Application No.	Applicant(s)	
	10/019,164	METCALF, BENJAMIN J.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *9-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTTION

The response filed 7-12-03 has been entered into the record.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/141,061, filed 6-25-99. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after

compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

The information disclosure filed 5-30-03 has been considered. A initialed copy is enclosed.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Election/Restrictions

Applicant's election of Group I in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the term "a tightly regulated promoter". The term "tightly" is a measure of degree and comparison and neither the art nor the specification define the term as it relates to any other promoter. For example, if all promoters were not in some fashion regulated then all genes would be expressed all the time. Therefore, all promoters appear to be regulated in nature. The specification does not define "tightly regulated promoters" and does not teach the specific features of these promoters, such that the skilled artisan would be able to readily distinguish any regulated/inducible promoter of the art from those that are "tightly regulated". Further, it is noted that DNA can not be expressed in lipidated form and this limitation is not interpretable.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Anilionis et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988).

Anilines et al teach a plasmid containing an outer membrane protein of *Haemophilus influenzae* encoding a protein having 153 amino acids and an approximate molecular weight of 16,000 daltons which they call PBOMP-1 (see page 1, first full paragraph). The PBOMP-1 of Anilines et al is "P6" in light of Nelson et al that teaches that "P6" is *Haemophilus influenzae* protein having 153 amino acids and a calculated molecular weight of 16,089 daltons (page 131, column 2, second paragraph). The plasmid of Anilines et al is designated

pPX166 and expresses PBOMP-1 under regulation of the lac promoter in *Escherichia coli* JM1003 (page 81, lines 3-22). Anilines et al teach that PBOMP-1 as expressed by recombinant *E. coli* are lipoproteins (see page 71, lines 30-33). The plasmid of Anilines et al was transformed into and expressed in several *E. coli* strains including JM103 and HB101 (see page 81, lines 23-25). In regard to the limitation of "tightly regulated promoter" , the lactose promoter of the art meets this limitation in that expression of the PBOMP-1 was reportedly regulated by the lac promoter (i.e. expression is regulated by the presence or absence of the specific inducer).

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims above 1, 2 and 8, and in view of Guzman et al (Journal of Bacteriology, 177(14):4121-4130, 1995).

Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) is set forth *supra*. Anilines et al differs by not teaching a plasmid with PBOMP-1 and an arabinose inducible promoter or a T7 promoter. However, Anilines et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and hence,

expression of the gene and depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15).

Guzman et al (Journal of Bacteriology, 177(14):4121-4130, 1995) teach vectors for use in *E. coli* that are both positively and negatively modulated, have a high level of expression and comprise the arabinose PBAD promoter and are not expressed in the absence of the inducer arabinose. Guzman et al teach the vector pBAD18-cm (see Figure 1A, page 4122). pBAD18-cm is the same vector utilized in the instant application to express the P6 protein (page 16, line 17-24) from claimed plasmid pPX4020.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) of Anilines et al into any of the arabinose inducible vectors of Guzman et al including pBAD18-cm because Anilines et al teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and the vectors of Guzman et al meet these criteria. In the absence of any factual evidence demonstrating a protein or nucleic acid sequence difference between the nucleic acids encoding the P6 *Haemophilus influnzae* proteins of the prior art and the nucleic acid encoding the P6 *Haemophilus influnzae* protein of plasmid pPX4020, the subcloning of a known protein into a different expression vector is highly conventional and routine in the

art. Further, should a sequence difference be factually demonstrated in response to this office action, then Applicants are officially on notice that the claimed plasmid would necessarily be subject to a deposit requirement pursuant to 112, first paragraph.

Claims 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims above 1, 2 and 8, and in view of Mertens et al (Gene, 164:9-15, 1995).

Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) is set forth *supra*. Anilines et al differs by not teaching a plasmid with PBOMP-1 and an arabinose inducible promoter or a T7 promoter. However, Anilines et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and hence, expression of the gene and depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15).

Mertens et al (Gene, 164:9-15, 1995) teach vectors for use in *E. coli* that are provide for high-level of expression. The plasmid comprises the PT7 promoter. Mertens

et al teach that the decision as to which promoter to use can be based on various criteria, such a promoter strength and control, economy, ease of utilization or the conditions under which the promoter is to be used (e.g. temperature condition and choice of host strains or medium; page 9, column 2-page 10, column 1). Mertens et al teach that lambda Pl and PT7 are among the strongest promoters known in *E. coli*, then can be tightly regulated and allow a free choice of host strains or induction conditions. Mertens et al teach that the described vectors have the potential to considerably improve the expression level of other heterologous genes (page 14, column 1, last full paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) of Anilines et al into any of the pT7 containing vectors of Mertens et al because Anilines et al teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and the vectors of Mertens et al meet these criteria and Mertens et al teach that the PT7 containing vectors have the potential to considerably improve the expression level of other heterologous genes.

Claims 3, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims above 1, 2 and 8, and in view of Mertens et al (Gene, 164:9-15, 1995) and Novagen Inc., admittedly commercially available in specification page 15, line 34).

Anilines et al (WO 90/02557, published 22 March 1990) in light of Nelson et al (Infection and Immunity, 56(1):128-134, 1988) is set forth *supra*. Anilines et al differs by not teaching a plasmid with PBOMP-1 and an arabinose inducible promoter or a T7 promoter. However, Anilines et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription and hence, expression of the gene and depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15).

Mertens et al (Gene, 164:9-15, 1995) teach that the decision as to which promoter to use can be based on various criteria, such a promoter strength and control, economy, ease of utilization or the conditions under which the promoter is to be used (e.g. temperature condition and choice of host strains or medium; page 9, column 2-page 10, column 1). Mertens et al teach that lambda Pl and PT7 are among the strongest promoters

known in *E. coli*, they can be tightly regulated and allow a free choice of host strains or induction conditions.

Novagen Inc. teaches a commercially available vector pET-27b. This commercially available vector is the vector comprising the T7 promoter that was used in the instant specification in the construction of the claimed pPX4019 plasmid (specification page 15, line 34).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to subclone the PBOMP-1 (i.e. innately the P6 protein as evidenced by Nelson et al) of Anilines et al into the commercially available vector pET-27B of Novagen et al because Anilines et al teach that for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high level of transcription, Mertens et al teach that the PT7 is among the strongest promoters known in *E. coli*, can be tightly regulated and provide a free choice of host strains or induction conditions. In the absence of any factual evidence demonstrating a protein or nucleic acid sequence difference between the nucleic acids encoding the P6 *Haemophilus influnzae* proteins of the prior art and the nucleic acid encoding the P6 *Haemophilus influnzae* protein of plasmid pPX4019, the subcloning of a known protein into a different expression vector is highly conventional and routine in the art. Further, should a sequence difference be factually demonstrated in response to this office action, then Applicants are officially

on notice that the claimed plasmid would necessarily be subject to a deposit requirement pursuant to 112, first paragraph.

Status of Claims

Claims 1-8 stand rejected. Claims 9-17 are withdrawn from consideration.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555. The examiner can normally be reached on M-F 9:30pm-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645

Patricia A. Duffy, Ph.D.
November 23, 2003